by the present invention in contrast to the cited prior art. The above amendments to Claim 10 find explicit support in the specification at page 3, lines 18-27, while new claims 30 – 33 find support at page 4, lines 8-27 and page 5, lines 18-27. No new matter has been added.

**Summary of the Present Invention**

Applicant would like to provide the following brief summary to help distinguish the claimed invention from the cited art. The present invention is directed to improved drug delivery devices and, in particular, to biodegradable drug delivery devices that provide for the sustained and controlled delivery of a desired therapeutic agent to the ocular environment. As noted in the Background section of the specification, prior art biodegradable implants exhibit significant variances in release rate often resulting in dumping of active agent upon disintegration of the implant, a situation which is particularly problematic in the ocular environment. [*See* Spec. at pages 1-2]. In the ocular environment, the drug is typically washed out of the eye by tear action and/or eliminated into the general circulation fairly rapidly, and thus sustained and controlled release patterns are of paramount importance. Irregular release rates from prior art ocular implants leading to dumping of drug creates significant dosing problems, and hinders successful medical treatment of ocular diseases.

The present inventors solved this problem in the prior art through the provision of a biodegradable, sustained-release ocular implant having hydrophilic and hydrophobic components specifically combined in appropriate amounts so as to modulate each other's rate of release. The specification provides extensive teaching with respect to appropriate combinations of active agent and modulator, wherein the modulator is either an accelerator or retardant specifically chosen to counteract the hydrophobicity or hydrophilicity, respectively, of the active agent. [*See* pages 4-7]. Moreover, experimental data is provided to demonstrate the importance of modulating the release rate of the active agent from the implant based on its solubility or insolubility in aqueous environments such as the eye. [*See* Example 1, Figs. 1A & 1B]. Additionally, the inventors have also discovered and demonstrated for the first time that a second active agent may effectively serve as a release modulator for the first active agent, again by selecting a second active agent having opposite water solubility characteristics compared to the first active agent, which provides the further advantage of a combined therapeutic effect. [*See* Example 2, Figs. 2A-C]. Applicant has herein amended independent Claim 10 to clarify this distinction between the present invention and the cited prior art. As explained below, the prior art does not teach or suggest the deliberate selection and

combination of hydrophilic and hydrophobic compounds into a sustained release ocular implant in the concentrations contemplated by the presently-claimed invention

**Bernstein *et al.***

U.S. Patent No. 5,656,297 to Bernstein *et al.* discloses a biocompatible polymeric matrix having a biologically active agent dispersed therein, together with a metal cation component to modulate the release of the active agent from the matrix. The metal cation component is described as containing at least one kind of multivalent metal cation in a non-dissociated state and/or a dissociated state, including metal salts, metal hydroxides, and basic salts of weak acids having a metal cation. The patent teaches that both soluble and insoluble metal cation components can be used in the implant (*see* col. 5, lines 17-35), but does not explain or differentiate between the use of the two types. In contrast, the teachings of the present specification describe polymeric implants having specific combinations of hydrophilic and hydrophobic components which are deliberately selected so as to modulate each other's release. Independent Claim 10 has now been amended to more clearly set forth this distinction between Applicant's improved ocular implants and those described in the prior art, including in the Bernstein *et al.* patent. Since Bernstein *et al.* fails to teach or suggest a biodegradable implant wherein the release modulator is selected based upon the hydrophilicity or hydrophobicity of the active agent, as recited in amended Claim 10, it cannot anticipate or render obvious this aspect of the claimed invention.

Moreover, new Claims 30 – 33 have been added setting forth the specific types of release modulators contemplated by the present invention, *i.e.* retardants and accelerators, as well as preferred embodiments of both types appropriate for use in the ocular environment. In this regard, Applicant notes that the metal cation components described by Bernstein *et al.* were never disclosed or contemplated by Applicant for use in the presently-claimed invention. Indeed, metal cation compounds may be contraindicated for many *in vivo* applications, including specifically the ocular environment, where metal cation compounds may very well be toxic. Bernstein *et al.* provide only *in vitro* data relating to the effect of metallic salts on water uptake, glass transition temperature, film porosity and the like, with no data confirming that such compounds would not be problematic or toxic *in vivo*. Thus, despite the broad suggestion in Bernstein *et al.* that its implants may find use subcutaneously, intramuscularly, intraperitoneally, intradermally, intravenously, intraarterially, intrathecally and/or intranasally, Bernstein *et al.* provide no data to overcome the understandable hesitation of one skilled in the art with respect to the safety of the proposed compositions,

particularly for intraocular use, a use which is neither disclosed nor suggested by Bernstein *et al.* Claim 10 has also been amended to clarify the nature of the claimed implant as appropriate for ocular use and to further distinguish over the cited art.

**Shell *et al.***

The prior art previously relied upon by the Examiner similarly fails to disclose or suggest the presently-claimed invention. U.S. Patent No. 4,478,818 to Shell *et al.*, for example, also fails to describe a suitable composition having both the components and the release characteristics required by the present claims. The '818 patent does not disclose or suggest the incorporation of a release modulator as contemplated by the present invention, and there is clearly no disclosure or suggestion to combine distinct hydrophobic and hydrophilic agents together so as to modulate their release from an implant. Instead, Shell *et al.* teach an ocular insert comprising a steroid in two different forms. [*See* '818 Patent, Abstract]. In one embodiment, the two forms of the steroid are micronized and dispersed in a bioerodible polymer, such as polylactic acid, to form a bioerodible insert or particle. [*See* col. 11, lines 29-37]. Importantly, however, the patent teaches that the bioerodible insert or particle will generally "comprise 0 to 60 parts of the same steroid in two different forms . . . with the remainder of the insert or particle the bioerodible polymer." [col. 11, lines 40-45]. Thus, there is clearly no disclosure or suggestion of the incorporation of an additional release modulator into the bioerodible implant itself as contemplated by Applicants' invention. The bioerodible inserts of Shell *et al.* consist of the two forms of the steroid and the desired polymer.

Moreover, there is no discussion or even a suggestion that one should incorporate a release modulator to counterbalance the hydrophobic/hydrophilic nature of the therapeutic agent, as recited in the amended claims, so as to achieve a custom-tailored and relatively constant release profile. Shell *et al.* say nothing regarding the advantageous use of hydrophilic release modulators to counteract hydrophobic therapeutic agents in their bioerodible inserts, or vice-versa, and therefore clearly fail to negate the patentability of Applicant's invention. In fact, Shell *et al.* suggest with respect to the choice of steroid that hydrophilic and hydrophobic forms can be used interchangeably. [*See* col. 5, lines 23-35].

**Yim *et al.* and Sander *et al.***

U.S. Patent No. 5,385,887 to Yim *et al.* and U.S. Patent No. 5,356,629 to Sander *et al.*, which were also previously cited by the Examiner, are even less relevant than the disclosure by Shell *et al.*

Both Yim *et al.* and Sander *et al.* describe semisolid "pastes" of osteogenic proteins for use in effecting bone repair, which have biocompatible particles or proteins dispersed in a malleable polymer matrix. There is no suggestion in either patent of the controlled release of an active agent from an implant by combining hydrophilic and hydrophobic agents, so as to avoid large dosage fluctuations over time. There is also no description of an implant capable of sustained delivery of an active agent over a period of at least about three days. Thus, these patents fail to describe implants having the characteristics recited in the amended claims.

In fact, one of skill in the art would recognize that the compositions described by Yim *et al.* and Sander *et al.* are incapable of meeting the sustained- and controlled-release claim limitations of the present invention. In this regard, both patents teach that their respective implants are prepared by mixing the various dry components together, and then adding a suitable liquid medium to form the "moldable, wetted composition" of Sander *et al.* (col. 5, lines 39-42 & 61-68) or the "malleable implant" of Yim *et al.* (col. 11, lines 10-29). Thus, Sander *et al.* specifically teach the use of a hydrating medium such as water, saline solution or blood (col. 5, lines 43-60), while in Yim *et al.* the liquid medium can be either autogenous blood, as described at column 7, lines 1-25, or alternatively a diluent such as aqueous glycerol for use with the cellulosic materials described at column 7, lines 26-49. As one of skill in the art knows, the addition of a hydrating medium during the mixing step would start the degradation of the polymer matrix immediately, and the consequent release of the active agent from the composition. Thus, the release rate of any active agent included in the mixture would be entirely unpredictable.

As explained above, there is no explanation or suggestion in the cited prior art of how one could combine hydrophilic and hydrophobic agents in a biodegradable implant so as to provide a relatively constant rate of release for an extended period of time. Applicant therefore respectfully traverses the Examiner's anticipation rejection and requests withdrawal of the same.

**Conclusion**

Applicant respectfully submits that the above amendments and arguments fully resolve the Examiner's rejections. Allowance at an early date is therefore earnestly requested. Should the Examiner believe that any further obstacles to allowance remain, Applicant encourages the Examiner to contact the undersigned by telephone at (415) 781-1989 or by fax at (415) 398-3249. The Commissioner is hereby authorized to charge any additional fees, including extension fees, to Deposit Account No. 06-1300 (Order No. A-60179-1/DJB/TAL).

Dated: December 12, 2000

Todd A. Lorenz
Registration No. 39,754
FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP
Four Embarcadero, Suite 3400
San Francisco, California 94111

1030417